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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/053,871	04/01/98	PINSKY	D 51917-B

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EXAMINER	
DECLOUX, A	
ART UNIT	**PAPER NUMBER**
1644	11

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/053,871	Pinsky et al
Examiner	**Group Art Unit**
DeCloux, Amy	1644

☒ Responsive to communication(s) filed on *Jun 19, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-40* is/are pending in the applicat

Of the above, claim(s) *1-28, 31, and 32* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *29, 30, and 33-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-40* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendments, mailed 4-7-00 and 6-16-00 (Paper No. 7 and Paper No. 10), are acknowledged. Claim 29 has been amended. Applicant has added a new set of claims numbering 33-39. However, this newly added set of claims contains two claims which are numbered 36. So therefore the last four claims originally numbered 36, 37, 38 and 39 have been renumbered as 37, 38, 39 and 40, respectively. So Claims 33-40 have been added. Claims 1-40 are pending, claims 1-28 and 31-32 have been withdrawn from consideration by the examiner as being drawn to the non elected invention. Claims 29-30 and 33-40 are being acted upon presently.

2. The examiner appreciates the receipt of the Benedict et al document. The draftsman has reviewed the 26 sheets of formal drawings and a Notice of Draftpersons Patent Drawing review is attached to the instant office action. The application is in sequence compliance.

3. The rejections of record can be found in the previous Office Action mailed 10-7-99 (Paper No. 6). The 112 second paragraph rejection and the Insley 102b rejection are withdrawn. However, the Moller102(b) and 103(a) rejections are maintained as applied to newly amended claim 29 and its dependent claim 30.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 36 is not supported by the specification or by the claims as originally filed. There is no support in the specification or claims as originally filed for the recitation "of a mutein of Factor IX with both limitations of 1) consisting of "essentially" of amino acids 1-47 of Factor IX and 2) further comprises at least one amino acid substitution from wild type Factor IX sequence. With regard to the former limitation, it is noted that the specification discloses on page 16, line 7, "only" in place of "essentially". It is noted that "consists essentially of" is broader than "consists of". There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes **new matter.**

6. Claims 29-30 and 33-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments, mailed 4-7-00 (Paper No. 7), have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action mailed 10-7-99 (Paper No. 6).

Applicants assert that said claims are now enabled by their amendment to claim 29 which further characterizes the term "recombinant mutein" wherein the recombinant mutein comprises a substitution deletion or addition of one or more amino acids to wild-type Factor IX or Factor IXa resulting in reduced ability to convert Factor X to Factor Xa. However this newly added limitation still leaves an almost limitless number of muteins to consider. The specification provides guidance for making muteins of Factor IX which consist of amino acid substitutions of His221, Asp269 or Ser365, or muteins of Factor IXa which consist of amino acid substitutions of His41, Asp89 or Ser185. However, there is insufficient direction or guidance provided to assist one skilled in the art in the selection of **any** " protealytically inactive recombinant muteins" that are effective for inhibiting clotting but do not significantly impair hemostasis, nor is there sufficient evidence provided that **any** such muteins are effective for inhibiting clotting but do not significantly impair hemostasis as recited in newly amended claim 29, for **any** recombinant mutein of Factor IX which consists essentially of amino acids 1-47 of Factor IX as recited in newly added claim 36, nor for **any** recombinant mutein of Factor IXa which comprises a deletion of one or more amino acids of wild type Factor IXa as recited in newly added claim 38. It would require undue experimentation to produce and investigate all such possible muteins without more explicit guidance from the disclosure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of inhibiting of clot formation in the subject which does not significantly interfere with hemostasis when said muteins, broadly encompassed by the claims, are added to the blood administered to a patient.

Examiner agrees with Applicant's assertion that the MPEP states that applicant need not describe all actual embodiments and that applicants have provided working examples of muteins. However, the working examples disclosed in the instant specification comprise only a minute fraction of the huge number of claimed embodiments, and the scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970) The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of inhibiting of clot formation in the subject which does not

significantly interfere with hemostasis when said muteins, broadly encompassed by the claims, are added to the blood administered to a patient.

Examiner agrees with Applicant's assertion that proteolytically inactive muteins Factor IX or of Factor IXa where the recombinant mutein comprises a substitution, deletion or addition of one or more amino acid to wild type Factor IX or to factor IXa resulting in reduced ability to convert Factor X to factor Xa, are extensively described in the instant specification. Examiner also agrees with applicant's assertion that murine models of human diseases are widely used. However it is noted by the examiner that the working examples provided in the specification in the murine models were used in conjunction with chemical Factor IX which had been chemically modified by dansylation of the histidine of the active site, and there are no working examples of the above mentioned recombinant mutein, and accordingly although these mutations would likely destroy the active site of proteolysis, there is insufficient guidance form the specification to predict that said recombinant muteins would not significantly interfere with hemostasis. The predictability of which changes can be tolerated in a mutein's amino acid sequence and still retain the ability to inhibit clotting but not significantly impair hemostasis, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Also, minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

Minor structural differences among structurally related compounds or compositions, such as amino acid deletions of Factor IX and/or Factor IXa as recited in claims 35-38, such as amino acid substitutions in the active site of Factor IX comprising one or more of the following amino acids, Ser365, Asp269, and His221 of Factor IX as recited in claims 33-34 and 36-37, or such as amino acid substitutions in the active site of Factor IXa comprising one or more of the following amino acids, His41, Asp89, and Ser185 of Factor IXa, can result in substantially different biological or pharmacological activities affecting clot formation and hemostasis. Given the lack of guidance concerning the nature of the modifications associated with muteins that the skilled artisan could use as a guide in making said muteins; it would require undue experimentation to practice the claimed invention.

In view of the lack of predictability of the art to which the invention pertains,

undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting clotting but do not significantly impair hemostasis.

So due to the insufficient guidance in the instant specification regarding the effectiveness of the recombinant muteins, the insufficient working examples in animal models using recombinant muteins, and in view of the huge scope of the recombinant muteins, the invention as recited by claims 29-30 and 33-40 is not enabled.

Applicant's arguments have not been found persuasive and the rejection is maintained as applied to newly amended claim 29 and its dependent claim 30, as well as to the newly added claims 33-40.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

7. Claim 36 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The term "consisting essentially of" recited in claim 36 is a relative term which renders the claim indefinite because the specification has not stated what are the essential features of amino acids 1-47, and what are nonessential.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall

not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 29-30 and 33-36 and 38-40 are rejected under 35 U.S.C. § 102(b) as being anticipated by Moller et al. (CA 2,141,642, in PTO-1449).

Applicant asserts that Moller et al. teach fragments of Factor IX, not muteins of Factor IX as recited in the instant claims. However, examiner notes that claim 29 recites muteins as encompassing deletions of factor IX. A deletion of a full length wild type Factor IX at the carboxyl or amino terminals would produce a fragment of Factor IX. So therefore, the muteins recited in claim 29 and dependent claims 30, 33-35 and 38-40 encompass fragments of Factor IX which are taught by Moller et al. Moller et al teach a Factor IXa mutein which does not show coagulation activity and does not significantly interfere with hemostasis as a method to treat ischemic events encompassed by the claimed methods (see entire document, including pages 1-2). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced treatment of ischemic events associated with thrombotic disease using muteins (fragments) of factors IX and IXa.

Examiner agrees with the applicant that Moller et al do not teach specific amino acid substitutions. However, the open language of the instant claims and the use of "essentially" in claim 36, requires the inclusion of claims 33-36 and 38-40 in the instant rejection.

12. Claims 29-30 and 33-39 are rejected under 35 U.S.C. § 103 as being

unpatentable over Moller et al. (CA 2,141,642, in PTO-1449) in view of Brandstetter et al. (PNAS 92:9796-800, 1995) and Insley et al . (US Patent 4,711,848).

Applicant argues as discussed above that Moller does not teach a mutein of Factor IX. However as addressed above, muteins comprising deletions as recited in the instant claims, can yield fragments.

Applicant also argues that Brandstetter et al only suggest the use of their X-ray structures of Factor IXa as a framework for localizing the interaction sites involved in Xase function. However, the examiner points out that Brandstetter et al. teaches that catalytic residues SER 365 and HIS 221 are in the active site of the serine protease (see entire document, especially page 9797, paragraph three) and also teaches in the last line of their article that this information can be used to make testable predictions of sites suitable for mutagenesis experiments. Inhibitory recombinant muteins of Factor IXa containing substitutions of said two residues were disclosed in the instant specification and recited in the newly added claims.

Applicants assert that there is no motivation to combine Moller et al and Brandstetter et al. However it is noted by the examiner that Moller provides the motivation of using muteins comprising fragments of Factor IXa to treat thrombotic diseases and thus an ischemic event that occurred as a result of said ischemic disease. Brandstetter et al teaches the active site of Factor IXa which encompasses several of the amino acid residue changes recited in the instant claims and provides even more motivation in the last line of the article which says that this information can be used to make testable predictions of sites suitable for mutagenesis experiments.

There fore the rejection is maintained as applied to newly amended claim 29 and its dependent claim 30.

The newly added claims 33-39 are drawn to a method of inhibiting clot formation in a patient, which comprises adding an inactive recombinant mutein to inhibit clot formation but which does not significantly interfere with hemostasis.

Moller et al. teach the use of fragments of Factors IX and IXa, which do not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods (see entire document, including pages 1-2 and 20), but do not teach specific amino acid substitutions of Factors IX and IXa.

Brandstetter et al. teach the spatial distribution of variants of Factor IXa that have been identified in clinical studies in hemophiliacs, and in particular teaches the catalytic residues SER 365 and HIS 221 that are in the active site of the serine protease (see entire document, especially page 9797, paragraph three).

Insley et al. teach methods of making site specific mutants of AT and that altered forms of AT that could be clinically important for use in inhibiting blood clotting, as for an example, in the treatment of disseminated intravascular coagulation, (entire article, especially column lines 30-40).

Inhibitory recombinant muteins of factor IXa of said two residues were referred to in the instant specification.

In order to accomplish a successful method of inhibiting clot formation in a subject using an inhibitory Factor IXa or Factor IX that does not significantly interfere with hemostasis, the ordinary artisan at the time the invention was made, would have been motivated to use an inhibitory Factor IXa or IX that does not significantly interfere with hemostasis as illustrated by the Factor IX and IXa fragments taught by Moller et al. and encompassed by the claims 33-36 and 38-39, which as discussed above encompass deletions and therefore fragments of Factors IX and IXa. For the same purpose, one also would have been motivated to use the mutations in Factor IXa found in hemophiliacs, and the knowledge of amino acids in the active site, and x-ray structure of Factor IXa as taught by Brandstetter et al, who, in particular teaches the catalytic residues SER 365 and HIS 221, which are recited in claims 33 and 34, in order to make muteins containing specific amino acid substitutions in the active site as recited in claim 37, and/or deletions, as a substitute or as a modification for the inhibitory fragments of factors IX and IXa taught by Moller et al, said mutations being produced according to the method of making recombinant mutants of Factor IX as taught by Insley et al., because Brandstetter et al teaches in the last paragraph of the article that this information by understanding of molecular mechanisms underlying hemophilia in which clot formation is inhibited, and that this information can be used to make testable predictions of sites suitable for mutagenesis, and thus one can transform a wild type Factor X or Factor IXa into a factor which inhibits clot formation.

From the teachings of the reference and of that known and practiced by the ordinary artisan, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the

claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. .

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
Patent Examiner
September 11, 2000

David A. Saunders
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